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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,803	12/10/2004	Robert Ramage	62146(71526)	8946

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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,803	RAMAGE ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 8-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050919;20041210*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Sequence Listing filed October 2, 2007 is approved.

2. The abstract of the disclosure is objected to because the Abstract needs more detail as to specific pharmaceutical uses of the claimed peptide derivatives. Correction is required. See MPEP § 608.01(b).

3. With respect to the amendment filed October 2, 2007, the amendment instruction for the amendment to the paragraph on page 9, line 23 to page 19, line 1 (emphasis added by examiner) is incorrect. This particular amendment will need to be re-submitted in corrected form.

4. The disclosure is objected to because of the following informalities: At page 7, line 6, "naphthyl" is misspelled. At page 15, line 12, it is believed that "talk" should instead be "talc". The word "methoxybenzoic" is misspelled at, e.g., page 18, lines 8 and 16; page 19, lines 5 and 13; page 20, lines 1, 9, and 17; page 21, lines 5 and 13; page 22, lines 10 and 18; and page 23, lines 6 and 14. At page 24, line 2, "methylbenzhydrylamine" is misspelled. At page 22, line 2, "metoxy benzoicacid" should be changed to "methoxybenzoic acid". Appropriate correction is required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 8-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for peptide derivatives of general formula (I) in which Z-$(CH_2)_n$-CO- is 2-furylcarbonyl, does not reasonably provide enablement for the other claimed peptide derivatives. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope

with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. With respect to (1), the nature of the invention is peptide derivatives which are capable of activating PAR-2, and their therapeutic uses. With respect to (2), the Ferrell et al article (J. Clin. Invest., Vol. 111, pages 35-41) teaches that a compound meeting the requirements of Applicants' general formula (I) and possessing an N-terminal phenylacetyl group shows no PAR-2 activity up to 1 mM, whereas the same compound with an N-terminal 2-furoyl group is active as a PAR-2 agonist. See page 37, column 1, first full paragraph. With respect to (3), the relative skill of those in the art is high. With respect to (4), the pharmaceutical arts in general are unpredictable. Further, the Ferrell et al article shows that change of the N-terminal groups of compounds of Applicants' general formula (I) can eliminate PAR-2 agonist activity of the compounds. With respect to (5), Applicants' claims embrace peptide derivatives of general formula (I) comprising innumerable types of aryl and heteroaryl groups having any number and types of substituents. There is no common size, charge, or hydrophilicity/hydrophobicity among the claimed aryl and heteroaryl groups. With respect to (6) and (7), the only peptide derivatives which are disclosed to have been tested and whose activity is reported in the specification have an unsubstituted 2-furoyl group at the N-terminus. See page

10 of the specification. The specification does not disclose PAR-2 activity for any other peptide derivatives, including the one taught by the Ferrell et al article to be inactive. The specification does not provide any direction or guidance as to how peptides encompassed within the scope of general formula (I) and known not to have PAR-2 activity, e.g., the ASKH115 of the Ferrell et al article, can be made to act as a PAR-2 activating agent. With respect to (8), in view of the wide range of optionally substituted aryl and heteroaryl groups encompassed by the instant claims, and in view of the teachings of the Ferrell et al article that a change in the N-terminal group can eliminate PAR-2 activity, the quantity of experimentation necessary to practice the invention would be vast, because every single possible optionally substituted aryl and heteroaryl group would have to be tested in order to determine activity. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

6. Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no antecedent basis in the claims for the phrase "the decrease of lacrimal fluid secretion" in claims 8 and 9. It is suggested that "the" be deleted from each phrase.

7. Instant claims 1-5, 8, and 9 are deemed to be entitled under 35 U.S.C. 119(a)-(d) to the benefit of the filing date of UK 0213286.8 because the foreign priority document, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention.

Instant claims 10 and 11 are not deemed to be entitled under 35 U.S.C. 119(a)-(d) to the benefit of the filing date of UK 0213286.8 because the foreign priority document, under the test

of 35 U.S.C. 112, first paragraph, does not disclose treating a patient suffering from or susceptible to Sjogren's syndrome.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

9. Claim 10 is rejected under 35 U.S.C. 102(a) as being anticipated by the Ferrell et al article (J. Clin. Invest., Vol. 111, pages 35-41). The Ferrell et al article teaches administering the peptide ASKH95 to mice. See, e.g., the Abstract; page 37, Figure 2; and page 38, Figure 3. ASKH95 corresponds to Applicants' general formula (I) in which Z is a furyl group, n=0, AA_1-AA_2 is Lys-Val, and R is -OH. Because Applicants' claim recites treating a patient "susceptible to" dysfunction of masticatory, dysphagia, etc., Applicants' claim is interpreted as embracing a method of preventing the named diseases. Because the same active agent is administered to the same patient according to the same method steps, inherently dysfunction of masticatory, dysphagia, etc. will be prevented to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present between the method of the Ferrell et al article and Applicants' claimed method to shift the burden to Applicants to provide evidence that the claimed invention is unobviously different than the method of the Ferrell et al article.

10. Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 01/47556 in view of the Ferrell et al article (J. Clin. Invest., Vol. 111, pages 35-41). (The examiner relies upon U.S. Patent Application Publication 2003/0203849 as a translation for the WO Patent Application '556.) The WO Patent Application '556 teaches the treatment or prevention of dry eye, corneal ulcer, and conjunctivitis by administration of a PAR-2 peptide activator. See, e.g., claims 1, 2, 16, and 17. The WO Patent Application '556 does not teach a PAR-2 peptide activator which satisfies the requirements of Applicants' general formula (I). The Ferrell et al article teaches peptide ASKH95, a PAR-2 agonist which corresponds to Applicants' general formula (I) in which Z is a furyl group, n=0, AA_1-AA_2 is Lys-Val, and R is -OH. See, e.g., the Abstract and page 37, Figure 2. It would have been obvious to one of

ordinary skill in the art at the time Applicants' invention was made to use the PAR-2 agonist of the Ferrell et al article as the PAR-2 peptide activator required by the WO Patent Application '556 for the treatment or prevention of dry eye, corneal ulcer, or conjunctivitis, because the method of the WO Patent Application '556 is not limited to any particular PAR-2 peptide activator, and because the substitution of one known species for a known genus where the species is known to have the necessary PAR-2 activation activity is prima facie obvious.

11. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being obvious over Seiberg et al (U.S. Patent Application Publication 2003/0138388). Seiberg et al teach peptides of Formula I which correspond to Applicants' claimed peptide derivatives when, in Formula I of Seiberg et al, one of R_1 and R_2 is H and the other is $C(=O)E_1$ in which E_1 is phenyl, naphthyl, or C_{7-10} phenylalkyl; A_1-A_2-A_3-A_4-A_5-A_6 is Leu-Ile-Gly-Arg-Leu; and R_3 is OH or NH_2. In particular, Seiberg et al teach preferred embodiments in which one of R_1 and R_2 is H and the other is $C(=O)E_1$ (see paragraph [0030]); in which A_1-A_2-A_3-A_4-A_5-A_6 is Leu-Ile-Gly-Arg-Leu (see paragraph [0031]); and in which R_3 is OH or NH_2 (see paragraph [0031]). The peptides of Seiberg et al are combined with pharmaceutically acceptable carriers for in vivo administration (see, e.g., paragraphs [0038] - [00153]). Seiberg et al do not teach a specific peptide having this particular combination of substituents. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to make peptides according to Formula I of Seiberg et al in which one of R_1 and R_2 is H and the other is $C(=O)E_1$ in which E_1 is phenyl, naphthyl, or C_{7-10} phenylalkyl; A_1-A_2-A_3-A_4-A_5-A_6 is Leu-Ile-Gly-Arg-Leu; and R_3 is OH or NH_2; because such peptides are generically encompassed within Formula I of Seiberg et al; because one of R_1 and R_2 being H and the other being $C(=O)E_1$, A_1-A_2-A_3-A_4-A_5-A_6 being Leu-Ile-Gly-Arg-Leu, and

R_3 being OH or NH_2 are substituents present in preferred embodiments and peptides of Seiberg et al; because E_1 being phenyl, naphthyl, or C_{7-10} phenylalkyl is specifically recited by Seiberg et al; and because, with respect to the closest species of Seiberg et al, i.e. SEQ ID NOS:10, 14, 18, and 22 (see paragraph [0031]), the substitution of one hydrophobic acyl group for another would not have been expected to affect significantly the properties or activities of the peptides. There is no evidence of record showing that Applicants' claimed peptide derivatives possess any property or activity not possessed by the closest peptide species of Seiberg et al.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey E. Russel/
Primary Examiner, Art Unit 1654

JRussel
July 28, 2008